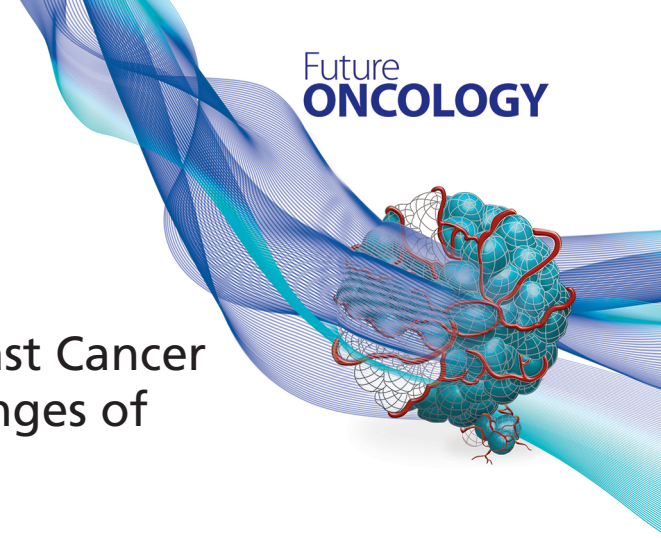
Conference Report

For reprint orders, please contact: reprints@futuremedicine.com



Highlights of the San Antonio Breast Cancer Symposium 2019 Part 1: the challenges of tumor heterogeneity

John R Benson*,[1], Dorin Dumitru[2] & Ismail Jatoi[3]

[1]Cambridge Breast Unit, Cambridge University Hospitals NHS Foundation Trust, & School of Medicine, Anglia Ruskin University, Cambridge, UK

[2]Breast Unit, Castle Hill Hospital Hull University Teaching Hospitals NHS Trust & Hull York Medical School, Hull, UK

[3]Division of Surgical Oncology, Dale H. Dorn Chair in Surgery, University of Texas Health Science Centre, San Antonio, 78229 TX, USA

*Author for correspondence: Tel.: +00 44 1223 586577; Fax: +00 44 1223 586932; john.benson@addenbrookes.nhs.uk

First draft submitted: 7 April 2020; Accepted for publication: 18 May 2020; Published online: 29 May 2020

Keywords: hormone replacement therapy • San Antonio • screening • stromal-epithelial interactions

The annual San Antonio Breast Cancer Symposium (SABCS) uniquely combines the principles of multidisciplinary management with the basic science underlying pathobiological processes in breast cancer. The 42nd meeting was held at the Henry B Gonzales Convention Centre in downtown San Antonio, Texas from 10–14 December 2019. The symposium delivers a range of presentations covering basic, translational and clinical sciences. Important trials that are potentially practice changing are often presented at SABCS and published concurrently or shortly thereafter. This is the first of a two-part report highlighting important presentations and focuses on topics relating to stromal–epithelial interactions, long-term outcomes of hormone replacement therapy and surgical management following neoadjuvant chemotherapy (NACT). Relevant background information is included where context appropriate.

Epidemiology/biology of breast cancer

In the first plenary lecture of the symposium Ellen Pure (University of Pennsylvania, PA, USA) discussed the role of stromal–epithelial interactions in breast cancer and in particular the importance of stromal cells and matrix remodeling in regulation of the tumor micro-environment. Understanding the dynamics of tissue organization within tumors and mechanisms underlying remodeling can provide insight into how tumors develop resistance to various therapeutic agents. Tumor carcinoma cells recruit additional cell types from the surrounding stroma to promote growth and allow a permissive or protumorigenic niche for both the primary tumor and cognate metastases [1]. Furthermore, the primary tumor can induce changes in distal target tissues such as the lung and bone marrow to influence disease progression. This occurs mechanistically through release of growth factors and other agents that enter the bloodstream and travel to distant tissues. Immune cells and adipocytes may have a key role in this conversation between primary tumor and distant metastases. It is now recognized that high mammographic density is a risk factor for breast cancer [2,3] and is a manifestation of a desmoplastic reaction induced in stromal tissues by carcinoma cells. These stromal elements provide mechanical support for tumors and constitute up to 90% of tumor bulk. This response is orchestrated by cancer-associated fibroblasts (CAF) which can influence many aspects of tumor cell behavior and malignant progression through provision of biochemical and biomechanical signaling [4]. In particular, these cells can have immunosuppressive effects as part of multifaceted tumor promoting activities. Through processes linked to factors such as aging, obesity and smoking, quiescent fibroblasts can be reprogrammed and transformed to activated fibroblasts that portend a worse prognosis. Nonetheless, activated fibroblasts are a heterogeneous group of cells and can be either tumor restraining or promote growth and stimulate cancer development. Different subsets of fibroblasts can be identified using specific cell markers. It was emphasized how therapeutic strategies should aim to promote a fibroblast restraining phenotype that typically has positive expression for smooth muscle antigen. Fibroblast activating protein (FAP) is a cell surface protein that influences epithelial-mesenchymal transition and is expressed in embryonic but not normal adult resting fibroblasts [5]. It

is a marker of CAF that categorizes a protumorigenic subpopulation. Targeting CAFs is technically challenging due to the complexity and context dependency of fibroblast function within tumors [6,7]. Interestingly, high levels of fibroblast fat expression are associated with a poor prognosis and a high fat diet is a risk factor for and likely contributes to breast cancer development through FAP mechanistically. Furthermore, fat-negative fibroblasts cannot support mammary matrix development while fat positive cells are tumor-enabled and expression of fat is an early carcinogenic event. Dr Pure speculated that fat could be a target for anticancer therapy and further research into other cell types such as pre-adipocytes and adipose-associated stromal cells is warranted.

Adoptive cell therapy using an FAP construct is currently being explored (FAP-CAR T cells). FAP in conjunction with a subset of activated fibroblasts promote tumor growth and targeting of molecular pathways that are dependent on CAFs is a potentially promising approach for maintenance of fibroblasts in a quiescent state. Deletion of functional FAP delays tumor progression independent of immune status and there is likely a 'stromagenic switch' that might be regulated for therapeutic benefit. Activation of this switch through pathways involving TGF-β and platelet-derived growth factor will induce a pre/prometastasis milieu; in contrast to carcinoma cells, the stroma is more genetically stable and less likely to develop drug resistance. Furthermore, FAP approaches may act synergistically with other targeted therapies, including immune modulation with minimal toxicities.

R Cheblowski (UCLA Medical Center, CA, USA) presented further data on the long-term influence of estrogen combined with progestin compared with estrogen alone on the incidence of breast cancer. Two Women's Health Initiative randomized trials have evaluated conjugated equine estrogen (CEE) alone or combined with medroxyprogesterone acetate (MPA) in postmenopausal women aged 50–79 years with or without a uterus [8,9]. Both of these trials recruited during the period 1993–1998 from 40 centers across the USA. Those women with an intact uterus were randomized to either CEE (0.625 mg/day) plus MPA (2.5 mg/day; n = 8506) or placebo (n = 8102) while hysterectomized women were randomly allocated to either CEE (0.625 mg/day) alone (n = 5310) or placebo (n = 5429). Follow-up for these two trials was 5.6 and 7.2 years, respectively, and the primary end point was time-specific invasive breast cancer incidence. Study medication was discontinued at the time of trial publication (2002 and 2004). The incidence of breast cancer was specifically examined during the postintervention period. For those women in receipt of CEE alone, the cumulative follow-up period was 16.1 years. In comparison with placebo, there was a 27% reduction in likelihood of being diagnosed with breast cancer and a 44% decrease in mortality from the disease. By contrast, for those women in receipt of CEE plus MPA, the cumulative follow-up period was 18.3 years. In comparison with placebo, there was a 29% increase in chance of being diagnosed with breast cancer together with an increased mortality from the disease (although this was not statistically significant). These trial results are counter-intuitive and have revealed opposite effects of CEE alone and CEE plus MPA on mortality that are long-term and persist for many years, even decades, after cessation of therapy. Notably, estrogen alone decreases but when combined with progestin, increases breast cancer incidence through patho-physiological mechanisms that remain elusive. There are potential implications for chemoprevention and improvements in all-cause mortality.

There has been resurgent interest in the androgen receptor (AR) as a therapeutic target in breast cancer patients. Among estrogen receptor (ER) positive patients, AR is a predictor of survival and various preclinical models are under development for clinical prediction of androgen sensitivity. Androgen inhibits proliferation of ER-positive breast cancer cells and E2-mediated regulation of cell cycle genes. E Lim (Garvan Institute of Medical Research, University of New South Wales, Sydney) discussed how strategies that enhance AR signaling by agonist effects will modify chromatin binding on the ER and demonstrably inhibit E2-driven growth of cell lines *in vitro*. Experiments with xenograft tumor models have shown more prominent cell inhibition with CDK 4/6 inhibitors in AR positive compared with AR negative tumors. The AR is the 'first point of call' and a promising prevalent target in hormone receptor positive disease.

Breast cancer screening

In 2007, the American Cancer Society issued guidelines for breast screening with MRI as an adjunct to mammography. In particular, the American Cancer Society recommended MRI screening for patients with a *BRCA-1* or *BRCA-2* gene mutation, untested first-degree relatives of BRCA mutation carriers, women with a lifetime breast cancer risk of at least 20% (based on validated risk-assessment models) and women in receipt of prior mantle chest irradiation between the ages of 10 and 30 years. However, the benefit of MRI as an additional screening modality to mammography alone has never been assessed in a randomized setting [10]. M Tilanus-Linthorst (Erasmus Medical Centre, Rotterdam, The Netherlands) presented results of a Dutch multicenter randomized controlled trial that recruited women with a cumulative lifetime risk for breast cancer of 20–50%. In this trial, women were randomized

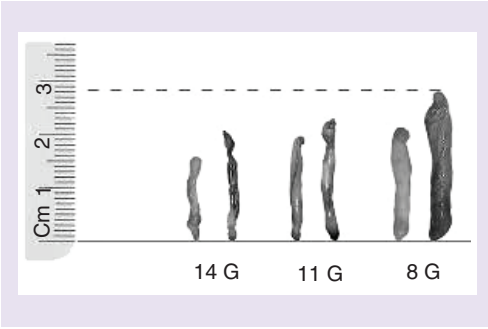


Figure 1. Significant variation in volume samples using different gauge needles (8–14).

to yearly screening with mammography plus clinical breast examination versus annual MRI together with biennial clinical breast examination plus mammography. Women with *BRCA-1*, *BRCA-2* or *p53* mutations were excluded from the study, as this group were already receiving MRI as an adjunct to mammography in the Netherlands. A total of 1355 women were randomized and at 7 years median follow-up, there were 40 cancers (both invasive and noninvasive disease) detected in the MRI group compared with just 15 cancers in the control group ($p < 0.002$). Moreover, cancers were smaller in the MRI group (9 vs 17 mm; $p = 0.01$) with proportionately more node positive cases in the mammogram group (63 vs 17%). Although screening with mammography plus MRI clearly increases breast cancer detection rates when compared with screening mammography alone, the impact on rates of mortality are not known. Nonetheless, use of MRI can potentially lead to a reduction in use of adjuvant therapies with corresponding cost savings.

Surgical management of breast cancer

When primary systemic therapy has eliminated any residual disease it might be argued that surgical excision of the tumor bed is redundant and confined to confirmation of pCR. This prompts the question of whether any tumor residuum can be identified without surgery using methods with a high negative predictive value (NPV). This might involve sampling of the tumor bed in exceptional responders for whom there is no clinical nor radiological evidence of residual disease. Percutaneous tumor bed biopsies can be performed under ultrasound-guidance with greater accuracy and performance parameters are likely to be influenced by size of the needle (standard or large gauge) and number of passes (Figure 1). A principle impediment to elimination of surgery after primary systemic therapy is the intrinsic limitations of standard and functional breast imaging. No current modality of imaging can predict residual disease with sufficient accuracy based on a sensitivity of >90% and a false-negative rate (FNR) of ≤10%. It is possible to integrate percutaneous needle biopsy of the breast tumor bed and axillary nodes in ways that complement imaging and more accurately predict residual disease. Presurgery biopsy of the tumor bed with combined fine-needle aspiration cytology and large volume, vacuum-assisted biopsy (VACB) under image guidance can reliably identify breast pCR with an accuracy of 98%, FNR of 5% and NPV of 95% [11]. This in turn may offer the opportunity of selectively eliminating breast and axillary surgery following NACT. Previous attempts to determine pCR pre-operatively with nonimage directed core biopsy and random sampling of the tumor bed were associated with high rates of local recurrence. Several ongoing and upcoming trials are evaluating the safety of eliminating breast (and axillary) surgery following chemotherapy in phenotype appropriate cases – namely TNBC and HER2 positive. These studies are likely to initially be confined to T1-2N0 tumors at presentation with demonstration of a complete or partial/near complete rCR on imaging. Percutaneous biopsy of the tumor bed can be carried out with either large gauge (VACB) or standard core biopsy. Absence of any residual disease on imaging or tumor bed biopsy would permit omission of breast surgery and possibly breast irradiation (i.e., no loco-regional treatment), while any evidence of residual disease would be an indication for standard therapy with surgery and irradiation.

There are four key questions to consider in the context of response-adjusted surgical management [12]. First, what are the performance characteristics of diagnostic tools used to predict pCR postchemotherapy? Second, what is the least morbid method to confirm or exclude residual disease in the breast and axillary nodes? Third, what are the consequences in terms of clinical outcomes if any minimal residual disease is missed and a 'watch and wait' policy is adopted? Finally, how should clinical trials be designed and conducted in order to provide robust evidence to

Table 1. Rates of local recurrence and survival in trial comparing accelerated partial breast with whole breast irradiation.

Characteristics	APBI	Whole breast irradiation
Ipsilateral breast tumor recurrence (10 years)	3.9%	2.6%
Ipsilateral breast tumor recurrence (5 years)	2.4%	1.2%
Overall survival (10 years)	92.7%	93.3%
Breast cancer-specific survival (10 years)	97.6%	97.5%
Disease metastatic-free survival (10 years)	96.9%	96.9%

APBI: Accelerated partial breast irradiation.

support changes in clinical practice? There were several presentations at SABCS2019 that addressed these questions and results were sobering.

M Tsoulis (Royal Marsden Hospital, London, UK) reported on a multi-institutional pooled analysis of patient level data for image-guided tumor bed biopsy post-NACT. A total of 166 patients were included with a mean tumor size pre-NACT of 33.5 and 10 mm after chemotherapy. All tumors without residual calcification or residual mass had marker clip insertion and the overall pCR rate was 51%. Tumor bed biopsy was undertaken in the majority of cases (86%) with VACB and ultrasound (78%) or stereotactic (14%) guidance. The mean needle gauge used for biopsy of the tumour bed in this pooled analysis was 10 (range 7–14) with a mean number of 6 (range 2–18) passes for each procedure. This study reported an overall FNR of 18.7% that was lowest for hormone receptor positive/HER2 negative (10%) and TNBC (11.6%) and highest for hormone receptor positive/HER2 positive tumors (33.3%). The NPV was 84.3 (95% CI: 76.7–91.8). A 'planned' subgroup analysis that was confined to patients (n = 76) with invasive ductal carcinoma, a tumor residuum $\leq$2 mm and retrieval of at least six cores found a FNR of 3.2% (95% CI: 0–8.8) and NPV 97.4% (95% CI: 84.6–99.6). However, this was a retrospective study that precludes any formal 'planned' analysis. Despite this promising pooled study, other data presented from three individual studies do not support breast conservation therapy after NACT without surgery.

The first of these negative studies was the RESPONDER trial presented by J Heil (University Hospital, Heidelberg, Germany). This trial evaluated 452 patients with a range of tumor types (TNBC [33%], HER2 positive [34%] and hormone receptor positive/HER2 negative [33%]) and partial or complete response to NACT. The final analysis was performed on 398 patients (54 exclusions). All patients underwent image-guided VACB with a broad range of larger gauge needle sizes (10G = 31%; 9G = 6%; 8G = 50%; 7G = 13%) and a mean number of 7 passes. Patients proceeded to breast surgery after NACT if tumor cells were present in the biopsy material or there was a sampling error (10% cases had a nonrepresentative biopsy pathologically). Patients without evidence of tumor cells on needle biopsy received breast irradiation only as definitive local treatment to the breast. The overall FNR was 17.8% (95% CI: 12.8–23.7) and residual tumor was missed in 37 out of 208 women. About half of these cases were considered to have minimal residual tumor (54.1%) and low residual invasive tumor content of $<$10% was recorded in three-quarters of patients with residual disease after NACT. Subgroup analysis on those biopsy cases performed with the largest needle size (7G) revealed a FNR of 0%, albeit with wide confidence intervals (95% CI: 0–18.5). Furthermore, when there was no evidence of residual disease in the breast either on imaging or tumor bed biopsy, the FNR was only 6.2%. It was concluded that up to half of these false-negative cases were attributable to 'avoidable causes' and optimization of technique could yield an acceptable overall FNR for prediction of residual tumor in the future.

The NRG – BR005 Phase II trial was designed to assess the accuracy of tumor bed biopsies in predicting pCR in patients with a complete or near complete imaging response post-NACT. In particular, the trial asked whether addition of tumor bed biopsies to clinical examination and tri-modality imaging (MMG, US, MRI) can identify patients for whom formal breast conserving surgery can be safely omitted. The trial enrolled 105 patients with operable invasive ductal carcinoma (T1–3; Stage 1/IIIA) treated with NACT after insertion of a marker clip at the start of chemotherapy. A total of 98 patients were eligible for analysis and there was an *a priori* stipulated NPV $\geq$90%. Results of this study were reported by M Basik (Segal Cancer Centre, Jewish General Hospital, Montreal, Canada) on behalf of NRG and are shown in Table 1. The overall sensitivity for detection of residual disease with VACB was 50% (95% CI: 22.9–67.1) and NPV 77.5% (95% CI: 76.7–91.8). Sensitivity was dependent on tumor type and highest for HER2 positive (60.0%) and lowest for TNBC (36.4%). Hence the addition of tumor bed

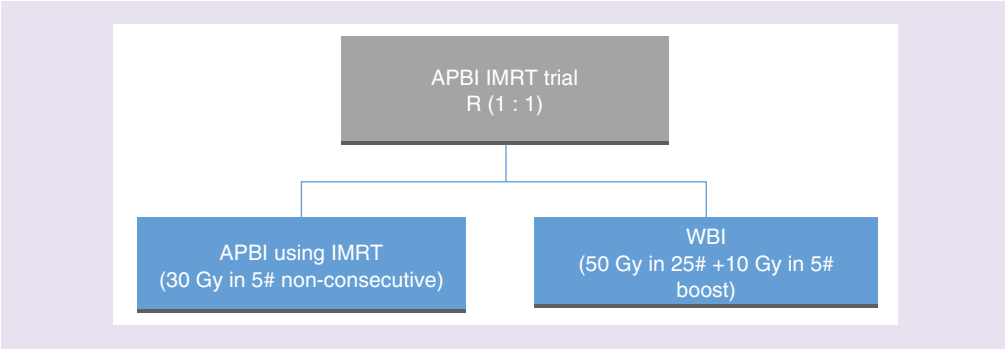


Figure 2. Schematic diagram showing design of the Florentine trial comparing accelerated partial breast with whole breast irradiation for early stage breast cancer patients.

Trial type
• Study arms
• Inclusion criteria
• Enrollment
• Study dates
• Primary outcomes
• Secondary outcomes
Phase III trial, randomized trial 1:1
• APBI using IMRT (30 Gy in 5# nonconsecutive)
• WBI (50 Gy in 25# + 10 Gy in 5# boost)
• Age >40 years
• Breast conserving surgery
• pT2 <25 mm
• Surgical margins >5 mm
• 520 patients
• March 2005–February 2014
• Ipsilateral breast tumor recurrence
• Early and late toxicity
• Clinician-rated cosmesis
• Overall survival
• Breast cancer-specific survival
• Contralateral breast cancer

APBI: Accelerated partial breast irradiation; IMRT: Intensity-modulated radiation therapy; WBI: Whole breast irradiation.

biopsy to tri-modality imaging failed to achieve a NPV of at least 90% and managed to identify only 50% of patients with residual disease at the time of surgery. Similar concerns about nonsurgical methods for detection of pCR after NACT were expressed by M-J V Peeters (Netherlands Cancer Institute, Amsterdam, The Netherlands) who was chief investigator for the Dutch MICRA (Minimal Invasive Complete Response Assessment) trial. This evaluated a combination of MRI and tumor bed sampling with standard core needle biopsy for prediction of response to NACT. All 167 patients recruited into the trial underwent MRI prior to starting chemotherapy. The majority of patients (n = 135) had a complete radiological response (rCR) with the remainder a partial response (n = 32). There was poor correlation between rCR and pCR – only 80 patients with rCR were found to have a corresponding pCR (59%). Therefore post-treatment tumor bed biopsy (14-gauge needle) missed residual tumor in more than a third of patients (37%) with a FNR of 45% for cases with rCR on MRI. Hence, neither standard core biopsy nor MRI was found to be sufficiently accurate to predict residual disease and the trial was closed prematurely. There was general consensus on importance of recognizing residual disease in order to offer further systemic treatment such as capecitabine or immunotherapy. With limited radiopathological correlation, there should be a cautious approach to abandoning comprehensive pathological assessment of the tumor bed after NACT (scattered foci of tumor may only be evident on immunohistochemistry).

Collective results of these studies indicate that currently it is inappropriate to abandon surgical excision of the tumor bed following NACT. The combined use of imaging and tumor bed biopsies cannot reliably identify partial responders and risks missing between a third and half of cases with residual disease. Nonetheless, refinements in patient selection and methods for tumor bed biopsy may yet improve key performance parameters (NPV, FNR) to within acceptable values.

Partial breast irradiation

I Meattini (University of Florence, Italy) presented 10-year follow-up results of the Phase III randomized trial of accelerated partial breast irradiation (APBI; 30 Gy to tumor bed in 5 daily fractions) or whole breast irradiation (WBI; 50 Gy in 25 fractions) following breast conserving surgery for early stage breast cancer patients (Figure 2 & Box 1). A total of 520 stage I and II breast cancer patients aged >40 years with tumors ≤25 mm were recruited between 2005 and 2013 with a 1:1 allocation to either APBI (intensity modulated radiotherapy) or WBI. There were no significant differences between these groups at 10 years in terms of ipsilateral breast tumor recurrence and survival parameters (overall, breast cancer specific and distant metastasis-free; Box 1). The rate of ipsilateral breast tumor recurrence was higher for the APBI group (3.9%) than the WBI group (2.6%) with a hazard ratio of 1.57. However, CIs were wide (0.56–4.41) and there was no statistically significant difference between the two groups (p = 0.39). Furthermore, both cosmetic scores and acute/late toxicity effects favored the APBI arm of the study. Based on these results, it was recommended that APBI should be more widely available and offered to postmenopausal women with hormone receptor positive and node-negative pT1 breast cancer. Indeed, APBI is now arguably a standard of care and an alternative radiation schedule to WBI in low risk early stage breast cancer patients.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1. Barcellos-Hoff MH, Medina D. New highlights on stroma-epithelial interactions in breast cancer. *Breast Cancer Res.* 7(1), 33–36 (2005).
2. Rice MS, Bertrand KA, VanderWeele TJ *et al.* Mammographic density and breast cancer risk: a mediation analysis. *Breast Cancer Res.* 18(1), 94 (2016).
3. Duffy SW, Morrish OWE, Allgood PC *et al.* Mammographic density and breast cancer risk in breast screening assessment cases and women with a family history of breast cancer. *Eur. J. Cancer* 88, 48–56 (2018).
4. Sahai E, Astsaturov I, Cukierman E *et al.* A framework for advancing our understanding of cancer-associated fibroblasts. *Nat. Rev. Cancer* 20(3), 174–186 (2020).
5. Park JE, Lenter MC, Zimmermann RN *et al.* Fibroblast activation protein, a dual specificity serine protease expressed in reactive human tumor stromal fibroblasts. *J. Biol. Chem.* 274(51), 36505–36512 (1999).
6. Allyson Lieberman, Barrett Richard, Kim Jaewon *et al.* Deletion of calcineurin promotes a pro-tumorigenic fibroblast phenotype. *Cancer Res.* 79(15), 3928–3939 (2019).
7. Santos AM, Jung J, Aziz N *et al.* Targeting fibroblast activation protein inhibits tumor stromagenesis and growth in mice. *J. Clin. Invest.* 119(12), 3613–3625 (2009).
8. Manson JE, Hsia J, Johnson KC *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N. Engl. J. Med.* 349(6), 523–534 (2003).
9. Hsia J, Langer RD, Manson JE *et al.* Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch. Intern. Med.* 166(3), 357–365 (2006).
10. Saslow D, Boetes C, Burke W *et al.* American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J. Clin.* 57(2), 75–89 (2007).
11. Keurer HM, Rauch GM, Krishnamurthy S *et al.* A clinical feasibility trial for identification of exceptional responders in whom breast cancer surgery can be eliminated following neoadjuvant systemic therapy. *Ann. Surg.* 267(5), 946–956 (2018).
12. Heil J, Keurer HM, Pfob A *et al.* Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: current evidence and future challenges. *Ann. Oncol.* 31(1), 61–71 (2020).